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Blood eosinophilia and ulcerative colitis - influence of ethnic origin

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Summary: **Blood eosinophilia is an alleged manifestation of ulcerative colitis. To investigate this association and to determine the effect of race, the occurrence of eosinophilia in all 44 Asians presenting between 1968–84 was compared to that in an age-and sex-matched group of indigenous white Caucasian patients presenting over the same period. Nineteen (43%) of the Asians presented with an eosinophilia compared to only 3 Caucasians ($P < 0.0001$); similar numbers (14 and 13) in both groups demonstrating transient eosinophilia on occasions during maintenance treatment although not related to clinical relapse. A control group of Asians with other disorders not known to be associated with eosinophilia did not manifest this abnormality on presentation although 3 patients did so transiently during out-patient observation.**

Eosinophilia is a feature of ulcerative colitis in many Asians possibly due either to an unusual racial response to ulcerative colitis or as a reflection of the underlying pathogenesis of their disease. We have not confirmed earlier suggestions of such a feature in white Caucasians. Eosinophilia occurring during maintenance treatment in both groups may be drug-related.

Introduction

Since 1950 there have been sporadic reports of blood eosinophilia in occasional patients with ulcerative colitis (UC) (Machella & Hollan, 1951; Riisager, 1959; Juhlin, 1963). Two later studies (Riis & Anthonisen, 1964; Wright & Truelove, 1966) also described eosinophilia, but either used a definition of eosinophilia ($> 0.2 \times 10^9/1$) which today would be regarded as too low, or gave no details of treatment or coexisting allergic disorders. None of these former studies, with the exception of that of Machella & Hollan (3 patients), documented circulating eosinophil counts at the initial presentation of disease. Thus there cannot be said to be an established relationship between eosinophilia and UC, the presence of which might (as has been inferred) reflect some underlying hypersensitivity mechanism involved in the bowel disorder.

Earlier studies have been based in the Western hemisphere so that nothing is known of the eosinophil response in other races, for example Asians, who constitute a sizeable proportion of the population in the UK. We have studied both indigenous white Caucasians and Asian immigrants with UC presenting to our unit to determine the presence of blood eosinophilia in this disorder and whether or not there is any racial influence.

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Patients and methods

Three groups of patients, A, B and C, were established retrospectively for the purpose of this study. Group A consisted of all 44 Asians (Indian and Pakistani) with an established diagnosis of UC. Patients from this group were matched for age and sex with 44 indigenous white Caucasians with UC, randomly extracted from a larger pool of patients presenting over the same period, who constituted group B and from whom identical details were obtained. Age randomization was achieved with a maximum variation of 3 years between matched pairs. To allow for the possibility of a racial predilection to eosinophilia a third group, group C, was formed consisting of age-and sex-matched Asians with various diagnoses excluding bowel- and eosinophilia-related disorders. Such patients were obtained from metabolic, respiratory, gastroenterology and paediatric files.

In groups A and B the diagnosis of UC was based on a compatible history and examination, sigmoidoscopic appearances, rectal or colonic histology, and radiological or colonoscopic examination of the large bowel. Subsequent sigmoidoscopic or colonoscopic

assessment with further tissue biopsies during indefinite follow-up, particularly in those patients with a short history or prolonged remission, confirmed the diagnosis of a non-infective colitis. Parasitic infestation with worms and protozoans (including *Entamoeba histolytica*), *Mycobacterium tuberculosis*, *Salmonella* and *Shigella* spp., *Yersinia enterocolitica* and *Campylobacter jejuni*, was rigorously excluded following extensive blood and fresh stool examinations (three or more specimens).

Details of the clinical, radiological, haematological and biochemical parameters of disease assessment in UC were obtained. These included the extent of colonic involvement – either procto-sigmoiditis, left-sided colitis or total/sub-total colitis, haemoglobin, white cell count and differential including absolute eosinophil count, number of counts per patient, erythrocyte sedimentation rate, serum orosomucoid and albumin. The course of disease, whether single episode, relapse-remitting or chronic continuous – was established for each patient as was the period of follow-up. The presence of atopic disorders (eczema, hayfever, asthma and allergies) was documented.

Data where appropriate were obtained during the period of active untreated disease at presentation. Eosinophil counts were additionally obtained at intervals during follow-up in all three groups and covering periods of remission and relapse of UC in groups A and B.

Eosinophil count

Differential white cell counts were undertaken on all patients with particular reference to absolute neutrophil and eosinophil numbers. Using samples of peripheral blood stored in EDTA preservative, leucocyte counts were obtained using either the direct 'wet' method of counting as described by Dacie & Lewis (1984), or a differential white cell count derived from a blood film and incorporating the total cell count using a Coulter Counter (Coulter Electronics Inc, Florida, USA). A neutrophilia was defined as an absolute count $> 7.5 \times 10^9/l$ and an eosinophilia as a count $> 0.44 \times 10^9/l$ (Dacie & Lewis, 1984). Although derived counts from blood films are less accurate than those from direct counting of diluted blood preparations (Nelson & Morris, 1984), this is only of significance at low or normal eosinophil levels whereas raised counts were the recorded data. The missing of borderline or slightly raised eosinophil levels in a few patients would apply equally to all three groups and would not influence data comparison.

Treatment

Patients referred with UC had, in many instances, received treatment from their own doctors. This consisted of various antidiarrhoeals (kaolin, codeine phosphate, diphenoxylate hydrochloride), antibiotics or analgesics. Three patients from group A and five from group B received empirical sulphasalazine at sub-therapeutic doses without effect on the symptoms, and none of the patients from either group received corticosteroids before diagnosis. Once the diagnosis of UC had been established patients received appropriate drug therapy. Maintenance treatment consisted of oral sulphasalazine with steroid retention enemas for active procto-sigmoiditis. More severe active disease was treated with systemic corticosteroids. Some patients also received a milk-free or milk-restricted diet to further alleviate symptoms. Re-assessment of disease at 6–24 month intervals included repeat barium studies or colonoscopies in those patients with active or extensive disease, and further biopsies of rectum or colon to establish chronicity and degree of activity.

Groups were analysed using fourfold tables (chi-square) for discrete variables and Student's t test for non-discrete variables. Where necessary, multiway frequency tables utilizing a log-linear model were used to analyse tables with higher frequencies of categories. Derived P values of < 0.05 were regarded as significant.

Results

Details of UC in patients of groups A and B are summarized in Table I. Radiological and laboratory data were comparable in both groups with the exception of the serum orosomucoid levels – a parameter of disease activity – which was significantly higher in group B. In addition not only was subsequent follow-up on average twice as long in group B, but also the subsequent course of disease differed; the predominant pattern in group A being of a single episode followed by a prolonged remission whereas in group B the patients experienced a relapse-remitting pattern.

The occurrence of eosinophilia in the three groups of patients at presentation is summarized in Table II. Eosinophilia was the predominant abnormality in Asian immigrants whereas in white Caucasians it was uncommon, neutrophilia being characteristic on presentation. No white cell abnormalities were detected at presentation in the Asian controls. The eosinophil count returned to normal levels within 12 weeks in those affected patients of group A, and reflected the progress to clinical remission.

During follow-up eosinophilia arose transiently at a similar frequency in groups A and B although this was not related to periods of active UC and the cell counts were only moderately elevated (Table III). In group A eight of the 19 patients presenting with an eosinophilia also demonstrated a raised level during follow-up,

Table I Disease parameters in Asians (group A) and Caucasians (group B) with ulcerative colitis

	Group A	*Group B*	*P value*
Age ± s.d. (years)	32.7 ± 13.2	33.9 ± 12.4	
Extent of disease:			
Procto-sigmoiditis	13	8	NS
Left sided colitis	11	11	NS
Total colitis	20	25	NS
Laboratory data (mean ± s.d.):			
Haemoglobin (g/dl)	12.4 ± 2.4	11.4 ± 2.4	NS
White cell count ($\times 10^9$/1)	9.1 ± 3.6	10.3 ± 3.4	NS
Albumin (g/l)	34 ± 8	33 ± 7	NS
ESR (mm/h, Westergren)	30 ± 28	41 ± 29	NS
Orosomucoid (g/l)	1.42 ± 0.62	2.0 ± 0.78	<0.001
Course of disease:			
Single episode	22	9	
Relapse-remitting	19	34	<0.005
Chronic-continuous	3	1	
Follow-up (years)	2.5 ± 2.2	5.0 ± 4.1	<0.01
Range	3 mo. – 9 yrs.	3 mo – 16 yrs.	

NS = not significant.

Table II Differential white cell counts and presence of circulating eosinophilia at presentation in Asians (44) and Caucasians (44) with ulcerative colitis, and Asian controls.

	Group A	*Group B*	*Group C*	*P value* (*A* vs *B*)
Period in UK (years)	11.7 ± 7.3	—	13.3 ± 7.6	
Patients with eosinophilia	19	3	0	< 0.001
neutrophilia	6	20	1	< 0.0001
normal differential count	19	21	43	
Mean (± 1 s.d.) eosinophil count of patients with eosinophilia ($\times 10^9$/1).	1.3 ± 0.5 ($n = 19$)	0.9 ± 0.4 ($n = 3$)	—	NS

NS = not significant

Table III Prevalence and magnitude of eosinophilia arising in patients with ulcerative colitis (UC) and Asian controls, during treatment and follow-up.

	Group A	*Group B*	*Group C*	*P value* (*A* vs *B*)
No. of counts per patient (mean ± 1 s.d.).	13 ± 11	15 ± 13	9 ± 5	NS
Patients with eosinophilia	14	13	3	NS
Eosinophilia during relapse of UC	6	5	—	NS
Mean (± 1 s.d.) eosinophil count of patients with eosinophilia ($\times 10^9$/1)	0.78 ± 0.18 ($n = 14$)	0.76 ± 0.27 ($n = 13$)	—	NS

NS = not significant

whereas two of the three affected patients in group B had a subsequent eosinophilia. However these latter patients also had well-documented additional allergic disorders (see below). Eosinophil counts were significantly lower than those obtained in Asians at presentation ($P < 0.02$). Three patients from group C also demonstrated a transient eosinophilia for no apparent reason, a lower frequency than that from group A ($\chi^2 = 8.82$, $P < 0.01$). Comparing those Asians presenting with and without eosinophilia in group A did not reveal any differences in laboratory parameters, colonic involvement or the subsequent course of disease; findings which extended to those patients from groups A and B who demonstrated eosinophilia subsequently.

Allergic disorders

In group A only one patient, who demonstrated both an initial and subsequent eosinophilia, was found with an atopic history – a perennial rhinitis. However in group B 11 patients (7 of whom demonstrated eosinophilia), revealed pre-existing disorders, *viz.* asthma (5), atopic eczema/urticaria (5), hayfever (2), nasal polyps (1) and allergic rhinitis (1), with 3 patients displaying concurrent disorders. One patient also suffered infestation with *Giardia lamblia* during an episode of eosinophilia.

Discussion

Earlier studies have suggested that eosinophilia is associated with UC and in particular with clinically active disease. Interpretation of these earlier reports is difficult for several reasons. Some studies involved few patients -3 to 12 (Machella & Hollan, 1951; Riisager, 1959; Juhlin, 1963), most patients studied had established, treated disease, treatment details were lacking, an atopic history excluding allergic disorders was not available (Riisager, 1959; Riis & Anthonisen, 1964; Wright & Truelove, 1966) and eosinophilia was often defined as only $> 0.2 \times 10^9/1$. Muehrcke *et al.* (1952) and Uhrbrand (1958) however have shown that the upper limit (at 2 s.d.) is $0.4 \times 10^9/1$ in normal populations because of large inter-personal variations in eosinophil levels and wide intra-personal diurnal alterations in normal individuals. As a result this latter value is in general use today; earlier studies would therefore include patients with eosinophil levels which would now be regarded as normal. The implied significance of a variation in eosinophil numbers within the normal range but reflecting alterations of activity in co-existing disease (Wright & Truelove, 1966) has not been substantiated.

Having taken these variables into account we have demonstrated a significant association between a circulating eosinophilia and active, untreated UC in Asian immigrants, but not in white Caucasians. The absence of eosinophilia in the Asian controls excluded a simple racial effect and a thorough search for parasites and other bowel pathogens eliminated the likely alternative for the blood disorder in this ethnic group. Two of the three Caucasian patients with a presenting eosinophilia had co-existent allergic disorders underlining the contrast between the two groups. Certainly compared to earlier studies (Hammer *et al.*, 1968; Pugh *et al.*, 1979) a high prevalence of allergic illnesses was present (25% *vs* 16%), whereas the Asian group contained a negligible number. In the latter instance cultural factors such as a poor command of English, particularly amongst females, and different concepts of allergic disease, may have given rise to a spuriously low figure. However this does not explain the large number of patients demonstrating an eosinophilia. The reasons for our findings were not related to the disease parameters that we assessed. Hypersensitivity mechanisms have been suggested (Jewell & Truelove, 1972) and this may be particularly relevant in Asian immigrants who are exposed to new dietary antigens in this country. An alternative explanation is that eosinophilia in Asians reflects some fundamental difference in the pathogenesis of UC, not evident in the parameters studied.

The transient eosinophilia arising following the implementation of treatment and disease remission was probably not disease related. It is unlikely that this would arise in treated disease in white Caucasians having not been evident initially, as well as arising similarly in six Asians. Furthermore, raised eosinophil numbers occurred equally during periods of active and quiescent disease implying a random occurrence, a feature accentuated in the white Caucasians by their longer period of observation and more active colitis. In these circumstances we would have expected a much higher frequency of eosinophilia if the suggestion of earlier studies, that raised numbers of eosinophils were associated with disease relapse, was to be borne out. It seems more likely that the treatment itself may have had a role either directly or indirectly. All patients received sulphasalazine, a drug known to induce hypersensitivity reactions often accompanied by marked eosinophilia (Chester *et al* 1978; Taffey & Das, 1983). It is conceivable that milder, sub-clinical reactions may occur reflected in modest and variable degrees of circulating eosinophilia. The concurrent use of steroid retention enemas, known to achieve significant blood levels (Powell-Tuck *et al*, 1976), would suppress this latter response (Kirsner & Palmer, 1954) thus reducing the potential magnitude. Paradoxically, this drug combination may also explain the anomaly of a high number of Asians presenting with an eosinophilia, but only a similar number to the white Caucasians developing a transient eosinophilia sub-

sequently. Drug treatment, by its direct action, would be expected not only to induce disease remission but also modify subsequent relapses, particularly with the eosinopoenic action of steroids. Many patients restarted corticosteroids at the time of relapse and before further blood estimations so that any resulting eosinophilia may have been reversed before clinical reassessment. Support for this explanation comes from the finding that less than half the Asian immigrants who presented with eosinophilia demonstrated this finding during treatment. Another reason was the relatively benign course of disease in the Asian immigrants with half the patients experiencing a continued remission following their initial episode.

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